

What is claimed is:

1. A freeze-drying microscope stage for screening an array of samples to identify processing parameters for freeze-drying, wherein the array comprises at least 24
5 samples, the freeze-drying microscope stage comprises:
 - at least one lyophilization plate comprising a plurality of stacked optically clear-layers;
 - a plurality of chambers in at least one lyophilization plate;
 - at least one pressure and temperature controlled chamber having optically-clear
10 windows; and
 - heating, cooling, and pressure controls connected to the freeze-drying microscope stage.
2. The freeze-drying microscope stage of claim 1, wherein the pressure controls enable providing a first pressure to a first sample in the array of samples and a
15 second pressure to a second sample in the array of samples.
3. The freeze-drying microscope stage of claim 2, wherein the first pressure is not equal to the second pressure.
4. The freeze-drying microscope stage of claim 1, wherein the heating and cooling controls provide a first temperature to a first sample in the array of samples and a
20 second temperature to a second sample in the array of samples.
5. The freeze-drying microscope stage of claim 4, wherein the first temperature is not equal to the second temperature.
6. The freeze-drying microscope stage of claim 5, wherein the heating and cooling controls enable controlling a temperature of the array of samples.
- 25 7. The freeze-drying microscope stage of claim 1, wherein the heating controls enable providing heat to a surface of one or more selected samples in the array of samples.
8. The freeze-drying microscope stage of claim 1, wherein the heating controls provide volumetric heating to one or more selected samples in the array of
30 samples.
9. The freeze-drying microscope stage of claim 6, wherein a plurality of samples in the array of samples, each sample comprising a freeze-dried fraction of a

common initial formulation, correspond respectively to a plurality of temperatures which enable a determination of a glass transition temperature of the freeze-dried fraction by observing flow of the freeze-dried fraction.

10. The freeze-drying microscope stage of claim 6, wherein the plurality of
5 samples in the array of samples are respectively maintained at a plurality of pressures whereby enabling identification of a first pressure from the plurality of pressures corresponding to a sample in the array of samples exhibiting a desired rate of freeze-drying.

11. The freeze-drying microscope stage of claim 9, wherein a structure of each
10 of the plurality of samples in the array of samples is examined before a freeze-drying cycle.

12. The freeze-drying microscope stage of claim 9, wherein a structure of each of the plurality of samples in the array of samples is examined during a freeze-drying cycle.

13. The freeze-drying microscope stage of claim 9, wherein a structure of each
15 of the plurality of samples in the array of samples is examined after a freeze-drying cycle.

14. The freeze-drying microscope stage of claim 6, wherein a plurality of samples in the array of samples comprise a formulation maintained at varying temperatures by the temperature control to determine a glass transition temperature of the
20 formulation.

15. The freeze-drying microscope stage of claim 6, wherein a plurality of samples in the array of samples comprise a formulation maintained at varying temperatures by the temperature control to determine a sublimation rate of the formulation.

16. The freeze-drying microscope stage of claim 6, wherein a plurality of
25 samples in the array of samples comprise a formulation are monitored to determine a moisture content of at least one sample in the plurality of samples.

17. The freeze-drying microscope stage of claim 1 including heating, cooling, and pressure controls to modify treatment of the array of samples.

18. The freeze-drying microscope stage of claim 1 further comprising multiple
30 optically-clear layers stacked to form an array of lyophilization chambers, at least one lyophilization chamber in a plurality of lyophilization chambers in the array of

lyophilization chambers having a port for introducing a sample and a port for evacuating air.

19. The freeze-drying microscope stage of claim 18 further comprising a master chamber for receiving stacked optically-clear plates forming an array of lyophilization chambers, the master chamber comprising at least one optically clear window to allow illumination of a sample in at least one lyophilization chamber.

20. The freeze-drying microscope stage of claim 18 further comprising a master chamber having ports for at least one member of the group consisting of vacuum, coolant, connection to a temperature sensor, connection to a temperature control device, and connection to a pressure sensor.

21. The freeze-drying microscope stage of claim 18 further comprising a cooling system having plates with integral cooling channels to provide a main cooling source, thermoelectric devices to provide fine temperature control and fins and plates to conduct heat relative to the samples in at least one lyophilization chamber.

22. The freeze-drying microscope stage of claim 18 further comprising a lighted microscope base and stand with adjustable positioning of at least one microscope objective.

23. The freeze-drying microscope stage of claim 18 further comprising a video camera to image samples in at least one lyophilization chamber.

24. The freeze-drying microscope stage of claim 23 wherein the video camera is a charge coupled device camera.

25. The freeze-drying microscope stage of claim 18, further comprising an X-Y positioning table to position a selected lyophilization chamber under a microscope objective.

26. The array of lyophilization chambers of claim 18, wherein there are at least 24 chambers.

27. The array of lyophilization chambers of claim 18, wherein there are at least 72 chambers.

28. The array of lyophilization chambers of claim 18, wherein there are at least 96 chambers.

29. The array of lyophilization chambers of claim 18, wherein there are at least 1000 chambers.

30. The array of lyophilization chambers of claim 18 wherein there are at least 10,000 chambers.

31. The array of lyophilization chambers of claim 18 wherein at least one chamber is a capillary.

5 32. The freeze-drying microscope stage of claim 1, wherein the lyophilization plate comprises three stacked optically clear layers.

33. The freeze-drying microscope stage of claim 32, wherein the three stacked optically clear layers consist of a top layer comprising a plurality of vapor evacuation ports, a middle layer comprising a plurality of sample placement regions, and a solid
10 bottom layer.

34. The freeze-drying microscope stage of claim 33, wherein there are at least 24 vapor evacuation ports and at least 24 sample replacement regions.

35. The freeze-drying microscope stage of claim 33, wherein there are at least 96 vapor evacuation ports and at least 96 sample replacement regions.

15 36. The freeze-drying microscope stage of claim 33, wherein there are at least 384 vapor evacuation ports and at least 384 sample replacement regions.

37. The freeze-drying microscope stage of claim 33, wherein there are at least 1536 vapor evacuation ports and at least 1536 sample replacement regions.

20 38. The freeze-drying microscope stage of claim 32, further comprising two windows to facilitate observation of samples contained therein.

39. The freeze-drying microscope stage of claim 32, further comprising lyophilization chamber sides.

40. The freeze-drying microscope stage of claim 32, further comprising a cooling assembly.

25 41. A method of screening an array of samples for evaluating suitability for freeze-drying comprising:

preparing at least 24 samples to form the array of samples, wherein at least two samples comprise a lyophilizable solvent;

freezing a plurality of samples in the array of samples;

30 subjecting the plurality of samples to a freeze-thaw cycle by thawing and refreezing;

subjecting the plurality of samples to a pressure in the range defined by at least 50 micrometers of Hg to no more than 760 millimeters of Hg; and

examining, visually, at least one sample in the plurality of samples to determine if the temperature has exceeded the glass transition temperature for the sample.

42. The method of claim 41 further comprising the step of freezing a sample
5 by supercooling.

43. The method of claim 42 further comprising the step of annealing the frozen sample by warming to about or below the melting point of the lyophilizable solvent for a first duration of time.

44. The method of claim 43 wherein the step of annealing includes warming
10 to no more than five degrees below the melting point of the lyophilizable solvent for the first duration of time.

45. The method of claim 43 wherein the step of annealing includes warming to no more than two degrees below the melting point of the lyophilizable solvent for the first duration of time.

46. The method of claim 43 wherein the first duration of time is at least an
15 hour.

47. The method of claim 43 wherein the first duration of time is at least five hours.

48. The method of claim 43 wherein the first duration of time is at least ten
20 hours.

49. The method of claim 43 wherein the first duration of time is less than fifteen hours.

50. The method of claim 41 further comprising the step of screening a range of temperatures below the melting point of the solvent for determining a corresponding
25 range of primary drying times.

51. The method of claim 50 further comprising the step of selecting a temperature corresponding to a desirable primary drying time from the range of primary drying times as an annealing temperature.

52. The method of claim 41 further comprising the step of screening a range
30 of temperatures below the melting point of the solvent for determining a corresponding range of secondary drying times.

53. The method of claim 52 further comprising the step of selecting a temperature corresponding to a desirable primary drying time from the range of secondary drying times as an annealing temperature.

5 54. The method of claim 41 further comprising the step of screening a range of temperatures below the melting point of the solvent for determining a corresponding range of primary and secondary drying times.

55. The method of claim 54 further comprising the step of selecting a temperature corresponding to a desirable primary and secondary drying time from the range of primary and secondary drying times as an annealing temperature.

10 56. The method of claim 41 wherein the step of freezing includes freezing at least one sample in a directional manner.

57. The method of claim 41 further comprising the steps of obtaining image data of the plurality of samples, and automatically processing the image data to identify samples exhibiting crystals having a desirable size distribution.

15 58. The method of claim 57 wherein the crystals are solvent crystals.

59. The method of claim 58 further comprising selecting conditions corresponding to formation of large crystals for preparing a sample.